# Complete Summary

## GUIDELINE TITLE

Breast cancer treatment.

## BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Breast cancer treatment. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2003 Jan. 45 p.

## COMPLETE SUMMARY CONTENT



## SCOPE

### DISEASE/CONDITION(S)

Early stage breast cancer: ductal carcinoma in situ and invasive breast carcinoma, stage 0, I, II

This guideline does not apply to lobular carcinoma in situ (lobular neoplasia) or invasive breast carcinoma greater than Stage II.

### GUIDELINE CATEGORY

Management
Treatment

### CLINICAL SPECIALTY

Nursing
Oncology
Plastic Surgery
Radiation Oncology

Radiology
Surgical Pathology

## INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Health Plans
Hospitals
Nurses
Physician Assistants
Physicians

## GUIDELINE OBJECTIVE(S)

- To improve access to all appropriate options for primary therapy for patients with early breast cancer
- To standardize the application of appropriate treatment modalities (surgery, radiation, and systemic therapy) and follow-up schedules for patients with breast cancer
- To increase the use of standardized education materials and psycho-social support for patients with breast cancer and their families
- To enhance awareness of the importance of clinical trials in breast cancer treatment

## TARGET POPULATION

All patients with the diagnosis of breast cancer (ductal carcinoma in situ, early stage [0, I, II] invasive breast carcinoma) who are candidates for treatment

## INTERVENTIONS AND PRACTICES CONSIDERED

1. Patient education
2. Biopsy, such as fine needle aspiration (FNA), needle core, or surgical (incisional or excisional). May also include radiographic (mammographic or ultrasonographic) localization
3. Bilateral mammogram or other breast imaging studies
4. Lumpectomy
5. Mastectomy
6. Axillary staging: axillary dissection and sentinel lymph node biopsy
7. Adjuvant chemotherapy
8. Breast reconstruction
9. Radiation therapy
10. Follow-up (annual mammograms, clinical breast examination, chest x-rays, serum chemistries, bone scans, soluble tumor markers, eye exams, and annual Pap and pelvic exams)

## MAJOR OUTCOMES CONSIDERED

- Rates of survival for patients receiving breast conservation treatment versus patients receiving mastectomy
- Incidence of breast cancer recurrence (relapse-free survival)
- Overall mortality rate
- Quality of life

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

### NUMBER OF SOURCE DOCUMENTS

Not stated

### METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

### RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system presented below, and are designated as positive, negative, or neutral to reflect the study quality.

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

Study Quality Designations:

The quality of the primary research reports and systematic reviews are designated in the following ways on the conclusion grading worksheets:

Positive: indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis.

Negative: indicates that these issues (inclusion/exclusion, bias, generalizability, and data collection and analysis) have not been adequately addressed.

Neutral: indicates that the report or review is neither exceptionally strong nor exceptionally weak.

Not Applicable: indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series

- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

## METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

## DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

## METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

## RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

## COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

## METHOD OF GUIDELINE VALIDATION

Clinical Validation-Pilot Testing
Internal Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Institute Partners: System-Wide Review

The guideline annotation, discussion, and measurement specification documents undergo thorough review. Written comments are solicited from clinical, measurement, and management experts from within the member groups during an eight-week review period.

Each of the Institute's participating member groups determines its own process for distributing the guideline and obtaining feedback. Clinicians are asked to suggest modifications based on their understanding of the clinical literature coupled with their clinical expertise. Representatives from all departments involved in implementation and measurement review the guideline to determine its operational impact. Measurement specifications for selected measures are developed by the Institute for Clinical Systems Improvement (ICSI) in collaboration with participating member groups following implementation of the guideline. The specifications suggest approaches to operationalizing the measure.

### Guideline Work Group

Following the completion of the review period, the guideline work group meets 1 to 2 times to review the input received. The original guideline is revised as necessary and a written response is prepared to address each of the responses received from member groups. Two members of the Committee on Evidence-Based Practice carefully review the input, the work group responses, and the revised draft of the guideline. They report to the entire committee their assessment of four questions: (1) Is there consensus among all ICSI member groups and hospitals on the content of the guideline document? (2) Has the drafting work group answered all criticisms reasonably from the member groups? (3) Within the knowledge of the appointed reviewer, is the evidence cited in the document current and not out-of-date? (4) Is the document sufficiently similar to the prior edition that a more thorough review (critical review) is not needed by the member group? The committee then either approves the guideline for release as submitted or negotiates changes with the work group representative present at the meeting.

### Pilot Test

Member groups may introduce the guideline at pilot sites, providing training to the clinical staff and incorporating it into the organization's scheduling, computer, and other practice systems. Evaluation and assessment occur throughout the pilot test phase, which usually lasts for three-six months. At the end of the pilot test phase, ICSI staff and the leader of the work group conduct an interview with the member groups participating in the pilot test phase to review their experience and gather comments, suggestions, and implementation tools.

The guideline work group meets to review the pilot sites' experiences and makes the necessary revisions to the guideline, and the Committee on Evidence-Based Practice reviews the revised guideline and approves it for release.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

The recommendations for the treatment of breast cancer are presented in the form of four algorithms, accompanied by detailed annotations. The Main Treatment algorithm has 26 components, while the Stage 0 Post-Surgical Treatment algorithm and the Stage I Post-Surgical Treatment algorithm each have five components and the Stage II Post-Surgical Treatment algorithm has six components; clinical highlights and selected annotations (numbered to correspond with the algorithms) follow.

Class of evidence (A-D, M, R, X) ratings and key conclusion grades (I-III, Not Assignable) are defined at the end of the Major Recommendations field.

## Clinical Highlights for Individual Clinicians

1. Breast cancer treatment involves a multidisciplinary approach including both primary and specialty care. From the first encounter with a patient and her family, mutual expectations and a trust relationship must be established. (Annotation 1, Main Treatment algorithm)
2. Appropriate treatment modalities must be applied and may include:
    a. Surgery (Annotations #16-21, Main Treatment algorithm)
    b. Medical oncology (Annotation #28 of the Stage 0 Algorithm, Annotation #33 of the Stage I Algorithm, and Annotation #38 of the Stage II Algorithm)
    c. Radiation oncology (Annotation #30 of the Stage 0 Algorithm, Annotation #35 of the Stage I Algorithm, and Annotation #41 of the Stage II Algorithm)

## Main Treatment Algorithm Annotations

1. Cancer Suspected or Proven

    The primary physician or specialist needs to confirm the presence or absence of cancer. This encounter is of critical importance, as it is at this time that the trust relationship is established. Mutual expectations are established and the steps are identified.

2. Education Regarding Options

    All potential options are reviewed with the patient and her significant other(s) when appropriate. It is important to include all possible treatment options (based on the biopsy results) at this visit. Breast conservation versus mastectomy as well as axillary staging options need to be discussed, including the rationale for the selection of the type of procedure. The anticipated cosmetic appearance should be discussed with the patient prior to choosing a surgical option.

    Reconstruction should be offered to women with Stage 0-II breast cancer who require or desire mastectomy.

    Consideration needs to be given to the resources that may be needed based on the type of surgery and/or degree of involvement. It is important to assist

the patient and her significant other(s) to have a seamless system of care. The following is a suggestion of services that the practitioner should consider:

- Patient education
- Radiation oncology
- General surgery
- Reconstructive plastic surgery
- Medical oncology

Evidence supporting this recommendation is of class: R

4. Biopsy

For palpable masses, fine needle aspiration (FNA), needle core, or surgical (incisional or excisional) biopsy may be performed. Non-palpable mammographic lesions require radiographic (mammographic or ultrasonographic) localization for either core needle or surgical biopsy.

Biopsy incisions should be placed to minimize subcutaneous tunneling when removing the tumor. Whenever possible, an incision should be situated so that it can be removed with a standard mastectomy incision. Curvilinear incisions following Langer's lines (concentric circles around the areola) provide the best cosmesis, especially in the upper hemisphere. Radial incisions will result in less tissue distortion when larger biopsies are performed in the lower half of the breast.

If cancer is suspected and the patient wishes breast conservation, a small margin of grossly normal breast tissue should be excised with the lesion. The specimen should be oriented with sutures or some other method to clearly define anterior-posterior, cephalad-caudad, and medial-lateral coordinates. The surgeon should examine the excisional specimen and remove additional tissue whenever inadequate tumor clearance is likely. Any additional specimen(s) must be oriented to indicate the new margin(s). Direct communication with the pathologist, whenever possible, is of enormous help.

Please refer to the Institute for Clinical Systems Improvement (ICSI) Diagnosis of Breast Disease guideline for information on specific biopsy procedures.

5. Is Cancer Present?

Review the biopsy report and, if cancer is present, initiate evaluation of the breast. If the biopsy is negative, refer to the NGC summary of the Institute for Clinical Systems Improvement (ICSI) guideline Preventive Services for Adults for follow-up.

7. Evaluation of the Breast

Bilateral mammogram within the past 6 months. Any other breast imaging studies would be at the discretion of the surgeon or radiologist.

8. Is Education Complete?

Review the record to determine if patient education is complete and appropriate for the stage that has been identified as a result of the biopsy and further studies.

10. Consultation(s) as Appropriate

Review the results of the biopsy, staging, education, and consultations that were previously done and determine if additional consultations are required.

13. Is Patient a Candidate for Breast Conserving Treatment?

Exclusion criteria for conservation management (outside of clinical trials):

- Diffuse microcalcifications
- Gross multicentric disease or gross multifocal disease
- Lesions >5 cm
- Inflammatory carcinoma
- Previous significant radiation treatment which included breast in the field
- Pregnancy is a relative contraindication.
- Collagen vascular disease including lupus and scleroderma are relative contraindications.

Note that exclusion based on age, central lesions, or histologic subtype is not appropriate.

The anticipated cosmetic appearance should be discussed with the patient prior to choosing any surgical option.

Patients with biopsy-proven invasive breast cancer may be eligible for neoadjuvant (pre-surgical) systemic therapy. For selected patients, neoadjuvant chemotherapy may make breast conservation feasible. Neoadjuvant therapy has not been shown to improve survival.

Evidence supporting this recommendation is of classes: A, B, R

14. Does Patient Choose Breast Conserving Treatment?

Breast conserving therapy is defined as excision of the primary tumor and adjacent breast tissue, followed by radiation therapy (XRT) of the whole breast or the breast and regional lymph nodes. Options and potential side effects are reviewed with the patient.

At this time, no subgroups have been defined in which XRT can be omitted. If the patient is on a protocol, then follow the protocol specifics as to the delivery of radiotherapy. Otherwise the following recommendations are made.

If chemotherapy is not to be given, XRT should be started in a timely fashion after conservative surgery is performed (usually within 2 to 4 weeks). XRT may be delayed if significant seroma is present, if a cellulitis is present, if arm range of motion is still limited, or if incisions are not healed. The best way to integrate XRT and chemotherapy in patients who are to receive both is not yet well defined. The two modalities have been given concurrently, sequentially, or in a sandwich fashion (i.e., chemotherapy both prior to and after XRT). Often all or a portion of chemotherapy is given initially.

Megavoltage radiation therapy is recommended to the whole breast using tangential fields (without bolus) treating to a dose of 4500 to 5000 cGy (180 to 200 cGy per fraction) over a 4 1/2 to 5 1/2 week period. This is usually followed by a boost of XRT to the area of the excisional biopsy for an additional 1000 to 2000 cGy. Omission of the boost may be associated with an increased risk of breast cancer recurrence, even in patients with negative margins.

Placement of surgical clips within the excisional biopsy site is encouraged in order to aid in improving XRT portal localization.

Regional (lymph node) radiotherapy is sometimes performed after breast conserving surgery including a level I/level II axillary lymph node dissection. Regional radiotherapy is controversial but frequently considered for patients with positive axillary lymph nodes, a positive high axillary lymph node, extranodal disease extension, or a large axillary lymph node; or if <6 lymph nodes were removed from the axilla without the aid of sentinel lymph node biopsy. Regional XRT is never recommended for stage 0 disease.

When done, regional XRT may include the supraclavicular, axillary, and internal mammary areas. If regional radiotherapy is given to the supraclavicular, axillary, or internal mammary areas, a dose of 4500 to 5000 cGy over a 4-1/2 to 5-1/2 week period is recommended. Special care must be taken where these fields abut one another and in the tangential breast fields. In the instance where a separate internal mammary field is used, a portion of the course should be given with an electron beam. When using deep tangential fields to treat the breast and internal mammary area, care must be taken to limit the amount of heart and lung within the fields.

Evidence supporting this recommendation is of classes: A, C, D, R

15. Does Patient Want Breast Reconstruction?

All patients should be advised about the possibility of breast reconstruction. If the patient is considering reconstruction, a referral to a reconstructive plastic surgeon is indicated. For more information, please refer to Annotation #18, "Mastectomy and Breast Reconstruction."

16. Mastectomy

If only cytologic diagnosis (e.g., fine needle aspiration specimen) of cancer has been obtained, a core-type biopsy to prove the diagnosis may be

considered if there is uncertainty based on cytology before proceeding with mastectomy. For open biopsy, a transverse or obliquely-oriented elliptical incision should be used, encompassing the biopsy skin incision whenever possible. Peripherally located biopsy sites may need to be excised separately. The nipple-areolar complex and all apparent breast tissue should be excised. Tumor involvement of the chest wall must be documented, widely excised and marked with clips to direct postoperative XRT.

If a patient is on a protocol which requires postoperative XRT, the XRT should be delivered according to the protocol specifics. Otherwise the following recommendations are made.

- Concerning the integration of post-mastectomy XRT and chemotherapy, a specific sequencing recommendation cannot be made. The two modalities have been combined in a number of ways, although often all or a portion of chemotherapy is given initially.
- Megavoltage XRT with a tangential field setup or an electron beam technique is recommended for treatment of the chest wall region itself to a total dose of 4500 to 5000 cGy (180 to 200 cGy per fraction) over a 4 1/2 to 5 1/2 week period. A boost of 1000 to 1500 cGy to the area of the primary site and/or chest wall scar region is also often performed. XRT should be delivered so as to minimize areas of dose non-uniformity within the treatment volume (e.g., use of appropriate energies, wedges, compensators, and tissue bolus) and the volume of lung and heart receiving a significant dose of radiation.
- In addition to chest wall, XRT to the supraclavicular area is usually performed. Consideration must also be given to the need for axillary and internal mammary XRT. The total dose delivered to the regional lymph node areas is approximately 4500 to 5000 cGy over a 4 1/2 to 5 1/2 week period. Special care must be taken in matching the supraclavicular field with the tangential or electron beam chest wall fields. The internal mammary field should be given with at least a portion using an electron beam. In addition, if using deep tangential fields to treat the chest wall and internal mammary area, care must be taken to limit the amount of heart and lung within the fields.

Evidence supporting this recommendation is of classes: A, B, C, D, R

17. Lumpectomy

The abnormality should be excised intact with a small margin of normal breast tissue and careful orientation for the pathologist (see Annotation #4 above). Except in rare and unusual circumstances, additional tissue should be removed so that negative microscopic margins are obtained. If additional tissue cannot be removed, patients with focally positive microscopic margins (defined as $\leq$3 low powered fields) can still be considered for breast conserving treatment. In instances of re-excisional biopsy, a thin margin of skin surrounding the incision and the entire biopsy cavity (if the site of involved margin(s) unknown) should be removed, orienting the specimen to allow the pathologist to define areas of involved resection margins precisely. Four to six metal clips at the base of the lumpectomy site will aid in directing the radiation therapy boost and not adversely affect radiologic follow-up.

Stage 0

Guidelines for lumpectomy for carcinoma in situ are similar to those for invasive cancers requiring all known disease to be removed by clinical, pathologic, and radiographic evaluation.

Stage I

With rare exceptions, all T1 tumors can be excised with grossly and microscopically clear margins and acceptable cosmesis if the patient desires lumpectomy. Subareolar tumors usually require excision of the nipple/areolar complex to achieve clear margins.

Stage II

Similarly, adequate tumor clearance and an acceptable cosmetic result can ordinarily be achieved following lumpectomy in patients with larger primary cancers.

Evidence supporting this recommendation is of classes: A, B, C, D

18. Mastectomy and Breast Reconstruction

When immediate reconstruction is to be performed by a reconstructive plastic surgeon, the general surgeon should complete the extirpative procedure without compromising oncologic surgical principles. Skin-sparing mastectomies are appropriate as long as there is an adequate anterior margin around the tumor and the previous biopsy incision is excised with the specimen. Injuries to the neurovascular bundles or fascial planes of the chest wall that are to be utilized in reconstruction should be avoided.

Implants/expander placement or free tissue transfer procedures can be used for immediate reconstruction. Cosmesis will be less satisfactory in patients who will receive post-mastectomy chest wall irradiation.

Evidence supporting this recommendation is of class: C

21. Axillary Staging
    A. Axillary Dissection

When axillary dissection is performed as part of a breast conserving operation, the procedure should usually be undertaken through a separate incision, preferably a transverse curvilinear incision within the anterior and posterior axillary folds rather than a vertical incision. In select and unusual cases, a separate incision may not be required. In these cases, the location of the primary tumor permits it to be excised through an incision placed posterior to the anterior axillary line. This same incision can also be used for performing the axillary dissection.

In any axillary dissection, all grossly involved lymph nodes should be excised but the tissues surrounding the axillary vein anteriorly and

posteriorly should be left intact to lessen the risk of lymphedema. All tissue caudad to the axillary vein and lateral to the medial border of the pectoralis minor should be excised. Injury or intentional transection of the medial pectoral, long thoracic, and thoracodorsal nerves for improved nodal clearance should be exceedingly rare. At completion of axillary dissection, a closed-system suction drainage catheter should be placed.

Axillary dissection includes Level I and Level II lymph node regions. The surgeon is advised to remove all grossly evident disease if possible. Lymph nodes fixed to one another or other structures are classified as N2 disease, making the tumor Stage III or greater. These findings should be included in the operative report.

Stage 0

Axillary dissection is not usually necessary for intraductal carcinoma in situ (DCIS). However, in large (>2.5 cm) non-invasive carcinoma, especially those with comedocarcinoma features or palpable lesions, invasive foci may be present. Consideration of axillary nodal sampling or partial axillary dissection should be given in these instances.

Stage I

Axillary sampling or dissection is routinely performed for clinical Stage I cancers primarily for staging purposes. In rare instances of small low grade cancers (i.e., tubular carcinoma <1 cm), particularly in elderly or debilitated patients with a benign axillary exam, axillary dissection may be omitted.

Stage II

Axillary sampling or dissection is routinely performed for Stage II breast cancers for staging the disease and regional control of tumor.

Evidence supporting this conclusion is of classes: C, R

B. Sentinel Lymph Node Biopsy (SLNB)

In sentinel lymph node biopsy (SLNB), blue dye and/or a radioactive isotope is injected into the area of the tumor. The first draining lymph nodes are identified and evaluated for the presence of metastases. If the sentinel nodes are free of cancer, additional lymph node removal may be avoided.

This approach requires a multidisciplinary team including surgeons, radiologists, pathologists, and oncologists with the experience and resources to perform the procedure and interpret results appropriately.

Numerous prospective validation studies confirm the accuracy of sentinel node biopsy in staging the axilla. Long-term survival data are not yet available.

Traditionally, axillary dissection has been the standard of practice. However, given the increasing experience and awareness of SLNB, with adequate experience and documentation of results it is becoming more widely accepted in medical practice. SLNB is appropriate for patients with a clinically negative axilla.

For more information about SLNB, please refer to Institute for Clinical Systems Improvement Technology Assessment #45 "Lymphatic Mapping with Sentinel Lymph Node Biopsy for Breast Cancer" (available from the Institute for Clinical Systems Improvement Web site).

Evidence supporting this conclusion is of classes: C, R

22. Is Staging Evaluation Complete?

Refer to the original guideline document for detailed recommendations for pathologic reporting.

## Stage 0 Post-Surgical Treatment Algorithm Annotations

(Excludes lobular carcinoma in situ.)

28. Oncology Visit
    - Review predicted risk of recurrence.
    - Adjuvant chemotherapy is not advised for stage 0.
    - Consider tamoxifen.
    - Encourage clinical trial participation.

30. Radiation Therapy Visit

Breast radiation therapy (XRT) following breast conserving surgery has been shown by randomized prospective data to improve local control in all subgroups identified. However, no difference in survival has been observed. If the patient is on a protocol, then follow the protocol specifics as to the delivery of radiotherapy. Otherwise the following recommendations are made.

Breast XRT should be started in a timely fashion after conservative surgery is performed (usually within 2 to 4 weeks). XRT may be delayed if significant seroma is present, if a cellulitis is present, if arm range of motion is still limited, or if incisions are not healed.

Megavoltage XRT is recommended to the whole breast using tangential fields (without bolus) treating to a dose of 4500 to 5000 cGy (180 to 200 cGy per fraction) over a 4 1/2 to 5 1/2 week period. This is usually followed by a boost of radiation therapy to the area of the excisional biopsy for an

additional 1000 to 2000 cGy. Omission of the boost may be associated with an increased risk of local recurrence, even in patients with negative margins.

Placement of surgical clips within the excisional biopsy site is encouraged in order to aid in improving XRT portal localization.

Although breast XRT is recommended for stage 0 disease, regional radiation therapy (to lymph node areas) is not.

Evidence supporting this recommendation is of classes: A, C, D

31. Follow-up Protocol

The guideline for follow-up refers only to the asymptomatic patient. New or persistent symptoms must be evaluated using whatever diagnostic studies are appropriate.

Use of chest x-rays, serum chemistries, bone scans, and soluble markers are not indicated for routine follow-up of patients with Stage 0 breast cancer. Patients who have Stage 0 breast cancer should be followed with yearly mammography. Clinical breast examination should be performed every 3 to 4 months for two years, then every 6 months for 3 more years in patients with Stage 0 breast cancer.

[Conclusion Grade I: See Discussion Appendix A of the original guideline document, Conclusion Grading Worksheet -Annotation #31 (Stage 0)]

Patients taking tamoxifen should have annual eye exams due to increased risk of cataracts and annual Pap and pelvic exams due to risk of endometrial carcinoma.

## Stage I Post-Surgical Treatment Algorithm Annotations

33. Oncology Visit
    - Review predicted risk of recurrence.
    - Encourage clinical trial participation.
    - Determine need for adjuvant therapy on individual case basis.
        - Characteristics to consider:
            - Pathologic prognostic factors predictive of less favorable outcome such as tumor size, high histologic grade, high nuclear grade, presence of lymphatic or vascular invasion
            - Overall health status
            - Menopausal status
            - Patient preferences
            - Receptor status
    - Coordinate all therapeutic plans with radiation therapy for patients electing breast conserving surgery.
    - Patient education about risks and benefits of chemotherapy and adjuvant therapy
    - Treatment options:

Estrogen receptor positive or progesterone receptor positive: Tamoxifen 20 mg daily for 5 years* + Chemotherapy**

Estrogen receptor negative and progesterone receptor negative: Chemotherapy** or observation

*Anastrozole can be considered in place of tamoxifen in post-menopausal women, especially those who may have contraindications to tamoxifen such as history of deep vein thrombosis (DVT), pulmonary embolism (PE) and stroke. Long-term data on benefits/risks of anastrozole are not yet available.

** NOTE: Chemotherapy may be advised as a treatment option for women of any age depending upon their overall health status and life expectancy, although minimal data are available on its advantages for women > age 70. Risk may be sufficiently low in some patients that chemotherapy would not benefit.

Chemotherapy should be administered by experienced physicians and/or personnel using established chemotherapy protocols and guidelines for dosage modifications.

- Currently accepted chemotherapeutic regimens in node-negative breast cancer include:
    - Doxorubicin/cyclophosphamide x 4 cycles
    - Cyclophosphamide/doxorubicin/5 fluorouracil x 6 cycles
    - Cyclophosphamide/methotrexate/5 fluorouracil x 6 cycles

Evidence supporting this recommendation is of classes: A, M

35. Radiation Therapy (XRT) Visit

At this time, no subgroups have been defined in which XRT can be omitted following breast conserving surgery. If the patient is on a protocol, then follow the protocol specifics as to the delivery of radiotherapy. Otherwise the following recommendations are made.

- If chemotherapy is not to be given, XRT should be started in a timely fashion after conservative surgery is performed (usually within 2 to 4 weeks). XRT may be delayed if significant seroma is present, if a cellulitis is present, if arm range of motion is still limited, or if incisions are not healed. The best way to integrate XRT and chemotherapy in patients who are to receive both is not yet well defined. The two modalities have been given concurrently, sequentially, or in a sandwich fashion (i.e., chemotherapy both prior to and after XRT). Often all or a portion of chemotherapy is given prior to XRT.
- Megavoltage XRT is recommended to the whole breast using tangential fields (without bolus) treating to a dose of 4500 to 5000 cGy (180 to 200 cGy per fraction) over a 4 1/2 to 5 1/2 week period. This is usually followed by a boost of XRT to the area of the excisional biopsy for an additional 1000 to 2000 cGy. Omission of the boost has been shown to increase the risk of local recurrence, even in patients with negative margins.
- Placement of surgical clips within the excisional biopsy site is encouraged in order to aid in improving XRT portal localization.

- Regional (lymph node) radiotherapy is not recommended for Stage I patients after conservative surgery including a Level I/Level II axillary lymph node dissection or a SLNB.

  Supraclavicular area ± axillary area XRT is controversial in patients with more limited axillary dissection (i.e., if <6 lymph nodes were removed from the axilla without the aid of SLNB). If regional XRT is given to the supraclavicular area ± axillary, a dose of 4500 to 5000 cGy over a 4 1/2 to 5 1/2 week period is recommended. Special care must be taken in matching the supraclavicular field with the tangential breast fields.

36. Follow-up Protocol

This guideline for follow-up refers only to the asymptomatic patient. New or persistent symptoms must be evaluated using whatever diagnostic studies are appropriate.

The use of chest x-rays, serum chemistries, bone scans, and soluble tumor markers are not indicated for the routine follow-up of patients with Stage I breast cancer and are not recommended outside of clinical trials.

Patients who have Stage I breast cancer should be followed with yearly mammography. Clinical breast examination should be performed every 3 to 4 months for 2 years, then every 6 months for 3 more years. Thereafter, medical care should be rendered according to routine health recommendations.

[Conclusion Grade I: See Discussion Appendix A of the original guideline document, Conclusion Grading Worksheet - Annotation #36 (Stage I)]

Patients taking tamoxifen should have annual eye exams due to increased risk of cataracts and annual Pap and pelvic exams due to increased risk of endometrial carcinoma. A baseline bone density should be considered for patients taking anastrozole and thereafter as indicated due to an increased risk of osteoporosis.

## Stage II Post-Surgical Treatment Algorithm Annotations

38. Oncology Visit

- Review predicted risk of recurrence.
- Encourage clinical trial participation.
- High dose chemotherapy with autologous stem cell or bone marrow support should not be used as part of the treatment of Stage II breast cancer outside participation in a randomized clinical trial.
- Coordinate all therapeutic plans with radiation therapy for patients following breast conserving therapy, as well as for those patients for whom post-mastectomy radiation therapy needs to be considered.
- Patient education about risks and benefits of chemotherapy and adjuvant therapy
- Treatment options

Estrogen receptor positive or progesterone receptor positive: Chemotherapy* + Tamoxifen 20 mg daily for 5 years**

Estrogen receptor negative and progesterone receptor negative: Chemotherapy* or observation

* NOTE: Chemotherapy may be advised as a treatment option for women of any age depending upon their overall health status and life expectancy, although minimal data are available on its advantages for women older than age 70.

Chemotherapy should be administered by experienced physicians and/or personnel using established chemotherapy protocols and guidelines for dosage modifications.

** Anastrozole can be considered in place of tamoxifen in post-menopausal women, especially those who may have contraindications to tamoxifen such as history of deep vein thrombosis, pulmonary embolism and stroke. Long-term data on benefits/risks of anastrozole are not yet available.

- Currently accepted chemotherapeutic regimens outside of clinical trials include:
  - Cyclophosphamide/methotrexate/5 fluorouracil x 6 cycles
  - Cyclophosphamide/doxorubicin/5 fluorouracil x 6 cycles
  - Doxorubicin/cyclophosphamide x 4 cycles
  - Doxorubicin x 4 cycles followed by cyclophosphamide/methotrexate/5 fluorouracil x 8 cycles
  - Doxorubicin/cyclophosphamide x 4 cycles, followed by 4 cycles of paclitaxel or docetaxel
  - Cyclophosphamide/epirubicin/5 fluorouracil x 6 cycles

Evidence supporting this recommendation is of classes: A, M

40. Is Postmastectomy Radiation Therapy (XRT) Indicated?

Literature indicates a role for postmastectomy XRT in improving locoregional control and survival for certain early stage patients with high risk features (and for patients with Stage III disease). These high-risk features include positive axillary lymph nodes (especially when $\geq$4 positive lymph nodes are present), pectoralis fascia involvement, primary tumor size $\geq$5 cm in maximal diameter, estrogen receptor negativity (when present in conjunction with other high-risk features), and positive surgical margins. Patients with extranodal disease extension, a positive high axillary lymph node, or a large axillary lymph node have been considered for postmastectomy XRT, although data to support this are lacking.

Evidence supporting this recommendation is of class: A

41. Radiation Therapy Visit

At this time, no subgroups have been defined in which XRT can be omitted following breast conserving therapy. If the patient is on a protocol, then follow the protocol specifics as to the delivery of radiotherapy. Otherwise the following recommendations are made.

If chemotherapy is not to be given, XRT should be started in a timely fashion after conservative surgery is performed (usually within 2 to 4 weeks). XRT may be delayed if significant seroma is present, if a cellulitis is present, if arm range of motion is still limited, or if incisions are not healed. The best way to integrate XRT and chemotherapy in patients who are to receive both is not yet well defined. The two modalities have been given concurrently, sequentially, or in a sandwich fashion (i.e., chemotherapy both prior to and after XRT). Often all or a portion of chemotherapy is given initially.

Megavoltage XRT is recommended to the whole breast using tangential fields (without bolus) treating to a dose of 4500 to 5000 cGy (180 to 200 cGy per fraction) over a 4 1/2 to 5 1/2 week period. This is usually followed by a boost of XRT to the area of the excisional biopsy for an additional 1000 to 2000 cGy. Omission of the boost has been shown to increase the risk of local recurrence, even in patients with negative margins.

Placement of surgical clips within the excisional biopsy site is encouraged in order to aid in improving XRT portal localization.

Regional (lymph node) radiotherapy is sometimes performed after breast conserving surgery including a level I/level II axillary lymph node dissection. Regional radiotherapy is controversial but frequently considered for patients with positive axillary lymph nodes, a positive high axillary lymph node, extranodal disease extension, or a large axillary lymph node, or if <6 lymph nodes were removed from the axilla without the aid of SLNB. When done, regional XRT may include the supraclavicular, axillary, and internal mammary area. If regional radiotherapy is given to the supraclavicular, axillary or internal mammary areas, a dose of 4500 to 5000 cGy over a 4-1/2 to 5-1/2 week period is recommended. Special care must be taken where these fields abut one another and the tangential breast fields. In the instance where a separate internal mammary field is used, a portion of the course should be given with an electron beam. When using deep tangential fields to treat the breast and internal mammary area, care must be taken to limit the amount of heart and lung within the fields.

Post Mastectomy Radiation Therapy

If a patient is on a protocol which requires post-mastectomy XRT, the XRT should be delivered according to the protocol specifics. Otherwise the following recommendations are made.

- Concerning the integration of post-mastectomy XRT and chemotherapy, a specific sequencing recommendation cannot be made. The two modalities have been combined in a number of ways, although often all or a portion of chemotherapy is given initially.
- Megavoltage XRT with a tangential field setup or an electron beam technique is recommended for treatment of the chest wall region itself to a total dose of 4500 to 5000 cGy (180 to 200 cGy per fraction) over a 4-1/2 to 5-1/2 week period. A boost of 1000 to 1500 cGy to the area of the primary site and/or chest wall scar region is also often performed. XRT should be delivered so as to minimize areas of dose non-uniformity within the treatment volume (e.g., use of appropriate

energies, wedges, compensators, and tissue bolus) and the volume of lung and heart receiving a significant dose of radiation.

- In addition to chest wall, XRT to the supraclavicular area is usually performed. Consideration must also be given to the need for axillary and internal mammary XRT. The total dose delivered to the regional lymph node areas is approximately 4500 to 5000 cGy over a 4-1/2 to 5-1/2 week period. Special care must be taken in matching the supraclavicular field with the tangential or electron beam chest wall fields. The internal mammary field should be given with at least a portion using an electron beam. In addition, if using deep tangential fields to treat the chest wall and internal mammary area, care must be taken to limit the amount of heart and lung within the fields.

42. Follow-up Protocol

This guideline for follow-up refers only to the asymptomatic patient. New or persistent symptoms must be evaluated using whatever diagnostic studies are appropriate.

The use of chest x-rays, serum chemistries, bone scans, and soluble tumor markers are not indicated for the routine follow-up of patients with Stage II breast cancer and are not recommended outside of clinical trials.

Patients who have Stage II breast cancer should be followed with yearly mammography. Clinical breast examination should be performed every 3 to 4 months for 2 years, then every 6 months for 3 more years. Thereafter, medical care should be rendered according to routine health recommendations.

[Conclusion Grade I: See Discussion Appendix A of the original guideline document, Conclusion Grading Worksheet - Annotation #42 (Stage II)]

Patients taking tamoxifen should have annual eye exams due to increased risk of cataracts and annual Pap and pelvic exams due to increased risk of endometrial and carcinoma. A baseline bone density should be considered for patients taking anastrozole and thereafter as indicated, due to an increased risk of osteoporosis.

Definitions:

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A

- Randomized, controlled trial

Class B

- Cohort study

Class C

- Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports

Class M

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness study

Class R

- Consensus statement
- Consensus report
- Narrative review

Class X

- Medical opinion

Conclusion Grades

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results from different studies

or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

### CLINICAL ALGORITHM(S)

Detailed and annotated clinical algorithms are provided for:

- Main Treatment Algorithm
- Stage 0 Post-Surgical Treatment Algorithm
- Stage I Post-Surgical Treatment Algorithm
- Stage II Post-Surgical Treatment Algorithm

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The guideline contains an annotated bibliography and discussion of the evidence supporting each recommendation. The type of supporting evidence is classified for selected recommendations (see "Major Recommendations").

In addition, key conclusions contained in the Work Group's algorithm are supported by a grading worksheet that summarizes the important studies pertaining to the conclusion. The type and quality of the evidence supporting these key recommendations (i.e., choice among alternative therapeutic approaches) is graded for each study.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

- Guideline implementation will help clinicians provide the best possible evaluation and treatment of patients with the diagnosis of breast cancer (ductal carcinoma in situ, early stage [0, I, II] invasive breast carcinoma).
- Breast conservation therapy is an appropriate method of primary therapy for the majority of women with stage I or II breast cancer and is preferable because it provides survival equivalent to total mastectomy and axillary dissection while preserving the breast.

### POTENTIAL HARMS

Not stated

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

These clinical guidelines are designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and are not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

Once a guideline is approved for release, a member group can choose to concentrate on the implementation of that guideline. When four or more groups choose the same guideline to implement and they wish to collaborate with others, they form an action group.

In the action groups, each medical group sets specific goals they plan to achieve in improving patient care based on the particular guideline(s). Each medical group shares its experiences and supporting measurement results within the action group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment, and tobacco cessation.

Detailed measurement strategies are presented in the original guideline document to help close the gap between clinical practice and the guideline recommendations. Summaries of the measures are provided in the National Quality Measures Clearinghouse (NQMC).

### RELATED NQMC MEASURES

- Breast cancer treatment: percentage of patients with Stage 0, I or II breast cancer with documentation in their medical record that the option of a clinical trial has been discussed with them.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Getting Better
Living with Illness

### IOM DOMAIN

Effectiveness
Patient-centeredness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Breast cancer treatment. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2003 Jan. 45 p.

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

1996 Sep (revised 2003 Jan)

### GUIDELINE DEVELOPER(S)

Institute for Clinical Systems Improvement - Private Nonprofit Organization

### GUIDELINE DEVELOPER COMMENT

Organizations participating in the Institute for Clinical Systems Improvement (ICSI): Affiliated Community Medical Centers, Allina Medical Clinic, Altru Health System, Aspen Medical Group, Avera Health, CentraCare, Columbia Park Medical Group, Community-University Health Care Center, Dakota Clinic, ENT Specialty Care, Fairview Health Services, Family HealthServices Minnesota, Family Practice Medical Center, Gateway Family Health Clinic, Gillette Children's Specialty Healthcare, Grand Itasca Clinic and Hospital, HealthEast Care System, HealthPartners Central Minnesota Clinics, HealthPartners Medical Group and Clinics, Hutchinson Area Health Care, Hutchinson Medical Center, Lakeview Clinic, Mayo Clinic, Mercy Hospital and Health Care Center, MeritCare, Mille Lacs Health System, Minnesota Gastroenterology, Montevideo Clinic, North Clinic, North Memorial Care System, North Suburban Family Physicians, Northwest Family Physicians, Olmsted Medical Center, Park Nicollet Health Services, Pilot City Health Center, Quello Clinic, Ridgeview Medical Center, River Falls Medical Clinic, Saint Mary's/Duluth Clinic Health System, St. Paul Heart Clinic, Sioux Valley Hospitals and Health System, Southside Community Health Services, Stillwater Medical Group, SuperiorHealth Medical Group, University of Minnesota Physicians, Winona Clinic, Ltd., Winona Health

ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; e-mail: icsi.info@icsi.org; Web site: www.icsi.org.

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## GUIDELINE COMMITTEE

Committee on Evidence-Based Practice

## COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Work Group Members: Lorre Ochs, MD (Work Group Leader) (HealthPartners Medical Group) (Oncology); John Donohue, MD (Mayo Clinic) (Surgery); Seth Wolpert, MD (HealthPartners Medical Group) (Surgery); Charles Loprinzi, MD (Mayo Clinic) (Oncology); Amy Spomer, MD (Park Nicollet Health Services) (Oncology); Robin Lally, RN, MS, AOCN, CNS (Park Nicollet Health Services) (Nursing) (Health Education); Joan Gunderson, RN, MS, CNS (HealthPartners Medical Group) (Nursing) (Health Education); Wayne Spears, MD (Minneapolis Radiation Oncology) (Radiation Oncology); Margaret Healey, PhD (Park Nicollet Institute) (Park Nicollet Health Services) (Measurement Advisor); Penny Carson (Institute for Clinical Systems Improvement) (Implementation Advisor); Mary Stadick, MA (Institute for Clinical Systems Improvement) (Facilitator).

## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

In the interest of full disclosure, the Institute for Clinical Systems Improvement (ICSI) has adopted a policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic. It is not assumed that these financial interests will have an adverse impact on guideline content. They simply are noted here to fully inform users of the guideline.

All work group members: none declared.

## GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Institute for Clinical Systems Improvement (ICSI). Breast cancer treatment. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2001 Aug. 38 p.

The next scheduled revision will occur within 18 months.

## GUIDELINE AVAILABILITY

Electronic copies of the revised guideline: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

## AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Breast cancer treatment. In: ICSI pocket guidelines. April 2003 edition. Bloomington (MN): Institute for Clinical Systems Improvement, 2003 Mar p. 304-6.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

## PATIENT RESOURCES

None available

## NGC STATUS

This summary was completed by ECRI on July 10, 2000. The information was verified by the guideline developer on April 25, 2001. This summary was updated by ECRI on April 15, 2002 and verified by the guideline developer as of June 3, 2002. This summary was most recently updated by ECRI on January 27, 2004.

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